

DESCRIPTION

AQUEOUS LIQUID PHARMACEUTICAL COMPOSITION

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FIELD OF THE INVENTION

The present invention relates to an aqueous liquid pharmaceutical composition comprising as a main component a quinolone carboxylic acid derivative, Gatifloxacin (chemical nomenclature: (\pm) -1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinoline carboxylic acid). Further, the present invention relates to a method for raising corneal permeability of Gatifloxacin, a method for preventing precipitation of Gatifloxacin crystals, and a method for preventing coloration of Gatifloxacin.

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BACKGROUND OF THE INVENTION

Gatifloxacin is a new quinolone antimicrobial agent which is recognized to exhibit a strong antimicrobial activity against not only Gram-negative bacteria but also Gram-positive bacteria, anaerobes and mycoplasmas. Then, it has been proposed to apply it to ophthalmological infectious diseases such as conjunctivitis, dacryocystitis, hordeolum etc. and otorhinological infectious diseases such as otitis externa, otitis media, sinusitis etc (see JP-B 8-9597).

For designing a pharmaceutical preparation in the form of eye drops containing an antimicrobial agent, an index is to raise corneal permeability of the agent to increase the amount of the agent to transfer to aqueous humor. However, in general, the agent applied to eyes can scarcely pass into inside of the eyes because of dilution with tears and the barrier function of corneas. Then, as a method of improving corneal permeability of the agent, a method using an absorption enhancer has been proposed. In addition, a method using a viscous base material has been proposed to increase the agent-retentivity at the anterior ocular segment.

OBJECTS OF THE INVENTION

With regard to Gatifloxacin, although its application to ophthalmological or otorhinological infectious diseases has been proposed, there is no report about a study of an aqueous liquid pharmaceutical composition thereof for topical administration, which can be actually applied to eyes, for example, its passing into inside of eyes, stability, etc.

In view of these circumstances, an object of the present invention is to permit actual application of Gatifloxacin in ophthalmological or otorhinological field, in particular, to provide an aqueous liquid pharmaceutical composition comprising as an effective component Gatifloxacin.

SUMMARY OF THE INVENTION

The present inventors have intensively studied to apply Gatifloxacin in ophthalmological field and, consequently, have found that this objective can be achieved by coexistence of Gatifloxacin with disodium edetate.

Disodium edetate is considered to lower the calcium concentration in corneal epithelium cells and expanding intercellular spaces, thereby accelerating passing of a water-soluble medicament into inside of eyes. However, a rise in corneal permeability of a medicament depends on a concentration of disodium edetate (Journal of Pharmaceutical Science, 77: 3-14, 1988) and, normally, at present, disodium edetate should be used at a high concentration as much as 0.5% (Investigative Ophthalmology & Visual Science, 26: 110-113, 1985; Experimental Eye Research, 54: 747-757, 1992; Pharmaceutical Research, 12: 1146-1150). Nevertheless, the present inventors have found that corneal permeability of Gatifloxacin can be improved at a lower concentration of disodium edetate.

Further, it has been known that the solubility of Gatifloxacin depends on pH and its solubility at about physiological pH is very low. Then, in order to dissolve a sufficient amount of Gatifloxacin in an aqueous liquid pharmaceutical composition, pH of the composition should be adjusted to an acidic or alkaline range, which causes a problem

such as irritation upon topical administration. However, the present inventors also have found that the solubility of Gatifloxacin at about physiological pH is improved by coexistence thereof with disodium edetate.

5 The present invention has been completed based on these present inventors' novel findings and, according to the present invention, there is provided an aqueous liquid pharmaceutical composition which comprises Gatifloxacin or its salt and disodium edetate. In particular, the aqueous liquid pharmaceutical
10 composition of the present invention is an aqueous solution containing Gatifloxacin or its salt and disodium edetate.

 Further, the present invention provides a method for raising corneal permeability of Gatifloxacin which comprises incorporating disodium edetate into eye drops containing
15 Gatifloxacin or its salt; a method for preventing precipitation of Gatifloxacin crystals which comprises incorporating disodium edetate into an aqueous liquid preparation containing Gatifloxacin or its salt; and a method for preventing coloration of Gatifloxacin which comprises incorporating disodium edetate into an aqueous
20 liquid preparation containing Gatifloxacin or its salt.

 This object as well as other objects and advantages of the present invention will become apparent to those skilled in the art from the following description.

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DETAILED DESCRIPTION OF THE INVENTION

In the present invention, Gatifloxacin or its salt is used as the effective component. Examples of the salt of Gatifloxacin used in the present invention include those with inorganic acids such as hydrochloric acid, sulfuric acid, phosphoric acid, etc.; those with organic acids such as methanesulfonic acid, lactic acid, oxalic acid, acetic acid, etc.; or those with sodium, potassium, magnesium, calcium, aluminum, cerium, chromium, cobalt, copper, iron, zinc, platinum, silver, etc.

Normally, the amount of Gatifloxacin or its salt (hereinafter sometimes simply referred to as "Gatifloxacin") to be formulated in the aqueous liquid pharmaceutical composition of the present invention is varied according to the degree of infection of a particular subject, but normally, Gatifloxacin is formulated within the range of 0.1 to 1.0 w/v%, preferably 0.1 to 0.8 w/v%, more preferably 0.3 to 0.5 w/v%.

Normally, disodium edetate is formulated in an amount of 0.001 to 0.2 w/v%, preferably 0.005 to 0.1 w/v%, more preferably 0.01 to 0.1 w/v%.

Normally, the aqueous liquid pharmaceutical composition of the present invention is adjusted to pH 5 to 8, preferably pH 5.5 to 7.5, more preferably pH 6 to 7.

If necessary, the aqueous liquid pharmaceutical

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composition of the present invention may further contain appropriate additives, for example, an isotonic agent (e.g., sodium chloride, potassium chloride, boric acid, glycerin, propylene glycol, mannitol, sorbitol, glucose etc.); a buffer solution (e.g., phosphate buffer solution, acetate butter solution, borate buffer solution, citrate buffer solution, glutamic acid, ϵ -aminocaproic acid, etc.); a preservative (e.g., benzalkonium chloride, benzethonium chloride, chlorhexidine gluconate, chlorobutanol, benzyl alcohol, sodium dehydroacetate, p-hydroxybenzoate, etc.), a thickening agent (e.g., methylcellulose, hydroxyethyl cellulose, hydroxypropyl methylcellulose, carboxymethylcellulose, sodium hyaluronate, carboxyvinyl polymer, polyvinyl alcohol, polyvinyl pyrrolidone, Macrogol (polyethylene glycol), etc.), a pH adjusting agent (e.g., hydrochloric acid, sodium hydroxide, acetic acid, phosphoric acid, etc.), and the like.

The aqueous liquid pharmaceutical composition of the present invention can be produced by a per se known method. For example, it can be produced by the process described in the section of "Ophthalmic Solutions" or "Liquids and Solutions", General Rules for Preparations, The Japanese Pharmacopoeia Thirteenth Edition.

The aqueous liquid pharmaceutical composition of the present invention has antimicrobial activity and can be used for prophylaxis and therapy of blepharitis, hordeolum, dacryocystitis, conjunctivitis, tarsitis, keratitis, corneal ulcer, postoperative

infection, and the like. For this purpose, the composition can be instilled in the eye about three times a day at a dosage of one drop per once. For otitis externa or otitis media, normally, the composition can be instilled in the ear twice a day at a dosage of 6 to 10 drops per once. Further, for sinusitis, normally, the composition can be sprayed and inhaled three times every other day in a week at a dosage of 2 to 4 ml per once, or can be administered in the maxillary sinus once a week at a dosage of 1 ml per once.

The dosage can be increased or decreased according to the degree of a particular disease condition.

The present invention will be further illustrated by the following experiments and examples, but the present invention is not limited thereto.

Experiment 1

Effect of disodium edetate on transfer of Gatifloxacin to aqueous humor

Method

According to the formulations of Table 1, eye drops of Gatifloxacin were prepared (formulations A-C). Each of the eye drops (50 μ l/eye) was instilled once in the eyes of male Japanese albino rabbits (body weight: about 2 kg). At one hour after the instillation, the aqueous humor was collected and the Gatifloxacin concentration was determined by HPLC.

Table 1

7.050

Formulations	A	B	C
Gatifloxacin	0.5 g	0.5 g	0.5 g
Disodium edetate	-	-	0.05 g
Sodium chloride	0.9 g	0.9 g	0.9 g
Hydrochloric acid	q.s.	q.s.	q.s.
Sodium hydroxide	q.s.	q.s.	q.s.
Sterilized purified water	to total 100 ml	to total 100 ml	to total 100 ml
pH	7.0	6.0	6.0

Results

The concentration of Gatifloxacin in the aqueous humor at one hour after the instillation is shown in Table 2.

When pH dropped, the amount of Gatifloxacin transferred to the aqueous humor decreased. For the formulation adjusted to pH 6.0 (formulation C), the amount of Gatifloxacin transferred to the aqueous humor increased by about 1.2 times and 1.5 times as much as those of the formulations A (pH 7.0) and B (pH 6.0) which were used as controls, respectively.

Since the concentration of disodium edetate normally used for raising corneal permeability is 0.5 w/v%, these results show that corneal permeability of Gatifloxacin has been improved even by using disodium edetate in 1/10 amount as much as that normally used.

Table 2

T.0100

Formulations	Gatifloxacin concentration in aqueous humor ($\mu\text{g/ml}$)
A	1.61 ± 0.43
B	1.30 ± 0.42
C	1.93 ± 0.95

Experiment 2

Effect of disodium edetate on precipitation of
5 Gatifloxacin crystals

Method

According to the formulations of Table 3, aqueous liquid preparations of Gatifloxacin were prepared (formulations B-D).

Each solution was filled in 5 ml glass ampoules. The ampoules were
10 subjected to freezing at -30°C (overnight) and then thawing at room temperature repeatedly to observe precipitation of Gatifloxacin crystals.

Table 3

T.0101

Formulations	B	C	D
Gatifloxacin	0.5 g	0.5 g	0.5 g
Disodium edetate	-	0.05 g	0.1 g
Sodium chloride	0.9 g	0.9 g	0.9 g
Hydrochloric acid	q.s.	q.s.	q.s.
Sodium hydroxide	q.s.	q.s.	q.s.
Sterilized purified water	to total 100 ml	to total 100 ml	to total 100 ml
pH	6.0	6.0	6.0

Results

15 In the formulation in which disodium edetate was not formulated (formulation B), crystals were precipitated when

freezing and thawing were repeated twice to three times. On the other hand, when disodium edetate was formulated (formulations C and D), no precipitation of crystals was recognized even when freezing and thawing were repeated ten times.

5 These results show that precipitation of Gatifloxacin crystals under storage conditions at a low temperature is prevented by formulating disodium edetate in an aqueous liquid preparation of Gatifloxacin.

Experiment 3

10 Effect of disodium edetate on preventing coloration of Gatifloxacin

Method

15 Sodium chloride (0.86 g) and 0.1 mol/liter hydrochloric acid (5.2 ml) were added to sterilized purified water (80 ml) in a stainless steel (SUS316) beaker of 8 cm diameter and the mixture was stirred. Then, Gatifloxacin (0.32 g) and disodium edetate (at a final concentration of 0%, 0.001%, 0.005%, 0.01% or 0.05%) were added thereto and dissolved therein. The solution was adjusted to pH 6.5 with 0.1 mol/liter sodium hydroxide and the total volume
20 was made up to 100 ml to obtain an aqueous liquid preparation of Gatifloxacin. A color difference between the aqueous liquid preparation and sterilized purified water was determined with a differential colorimeter (Chroma meter CT-210C manufactured by Minolta, light source Lab table system). As a control, an aqueous

liquid preparation of Gatifloxacin prepared in a glass beaker was used.

Results

The color difference determined is shown in Table 4.

5 The aqueous liquid preparation prepared in the glass beaker and used as the control had the color difference of 1.9 to 2.0 and a pale yellow color. On the other hand, the aqueous liquid preparation prepared in the stainless steel beaker had the color difference of 3.17 in case that disodium edetate was not added and 2.42 in case that 0.01% of disodium edetate was added. They had a light yellow color and a pale yellow color, respectively. Thus, they were discolored by formulating disodium edetate.

10 In view of these results, it is considered that Gatifloxacin is colored by the metal ion dissolved in the preparation from the stainless steel beaker. Further, these results show that addition of disodium edetate can prevent coloration of Gatifloxacin.

Table 4

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Concentration of disodium edetate (%)	Color Difference	
	Stainless Steel Beaker	Glass Beaker
0	3.17	1.90
0.001	3.08	1.93
0.005	3.05	2.02
0.01	2.42	1.94
0.05	2.19	1.93

According to a conventional method, an aqueous solution for eye drops, ear drops and nasal drops having the following formulation was prepared.

	Ingredients	Amount
5	Gatifloxacin	0.5 g
	Disodium edetate	0.1 g
	Sodium chloride	0.9 g
	Hydrochloric acid	q.s.
	Sodium hydroxide	q.s.
10	Sterilized purified water	up to 100 ml
	pH	7.0

Example 2

According to a conventional method, an aqueous solution for eye drops, ear drops and nasal drops having the following formulation was prepared.

	Ingredients	Amount
	Gatifloxacin	0.5 g
	Disodium edetate	0.05 g
	Sodium chloride	0.9 g
20	Hydrochloric acid	q.s.
	Sodium hydroxide	q.s.
	sterilized purified water	up to 100 ml
	pH	7.0

Example 3

According to a conventional method, an aqueous solution for eye drops, ear drops and nasal drops having the following formulation was prepared.

T.0140

	Ingredients	Amount
5	Gatifloxacin	0.5 g
	Disodium edetate	0.1 g
	Sodium dihydrogen phosphate	0.1 g
	Sodium chloride	0.9 g
	Hydrochloric acid	q.s.
10	Sodium hydroxide	q.s.
	Sterilized purified water	up to 100 ml
	pH	7.0

Example 4

According to a conventional method, an aqueous solution for eye drops, ear drops and nasal drops having the following formulation was prepared.

T.0141

	Ingredients	Amount
	Gatifloxacin	0.3 g
	Disodium edetate	0.05 g
20	Sodium chloride	0.9 g
	Hydrochloric acid	q.s.
	Sodium hydroxide	q.s.
	Sterilized purified water	up to 100 ml
	pH	6.0

Example 5

According to a conventional method, an aqueous solution for eye drops, ear drops and nasal drops having the following formulation was prepared.

5	Ingredients	Amount
	Gatifloxacin	0.5 g
	Sodium edetate	0.01 g
	Glycerin	2.6 g
	Benzalkonium chloride	0.005 g
10	Hydrochloric acid	q.s.
	Sodium hydroxide	q.s.
	Sterilized purified water	up to 100 ml
	pH	7.5

Example 6

According to a conventional method, an aqueous solution for eye drops, ear drops and nasal drops having the following formulation was prepared.

	Ingredients	Amount
	Gatifloxacin	0.5 g
	Sodium edetate	0.05 g
	Sodium chloride	0.9 g
	Hydrochloric acid	q.s.
	Sodium hydroxide	q.s.
	Sterilized purified water	up to 100 ml

pH

5.5

Example 7

According to a conventional method, an aqueous solution for eye drops, ear drops and nasal drops having the following formulation was prepared.

Ingredients

Amount

Gatifloxacin

0.3 g

Disodium edetate

0.05 g

Sodium chloride

0.9 g

Hydroxypropylmethyl cellulose

0.1 g

Methyl p-hydroxybenzoate

0.026 g

Propyl p-hydroxybenzoate

0.014 g

Hydrochloric acid

q.s.

Sodium hydroxide

q.s.

Sterilized purified water

up to 100 ml

pH

6.0

Example 8

According to a conventional method, an aqueous solution for eye drops, ear drops and nasal drops having the following formulation was prepared.

Ingredients

Amount

Gatifloxacin

0.5 g

Disodium edetate

0.01 g

Sodium chloride

0.83 g

	Benzalkonium chloride	0.005 g
	Hydrochloric acid	q.s.
	Sodium hydroxide	q.s.
	Sterilized purified water	up to 100 ml
5	pH	5.5

Example 9

According to a conventional method, an aqueous solution for eye drops, ear drops and nasal drops having the following formulation was prepared.

10	Ingredients	Amount
	Gatifloxacin	0.3 g
	Disodium edetate	0.01 g
	Sodium chloride	0.86 g
	Benzalkonium chloride	0.005 g
15	Hydrochloric acid	q.s.
	Sodium hydroxide	q.s.
	Sterilized purified water	up to 100 ml
	pH	6.0

As shown in Experiment 1, according to the eye drops of the present invention, corneal permeability of the effective component, Gatifloxacin, can be improved even by using disodium edetate in 1/10 amount as much as that normally used. Further, as shown in Experiment 2, the aqueous liquid preparation of the present invention can prevent precipitation of Gatifloxacin

crystals under storage conditions as a low temperature. Furthermore, as shown in Experiment 3, coloration of Gatifloxacin by a metal ion can be prevented. Thus, the aqueous liquid preparation of the present invention is very useful.